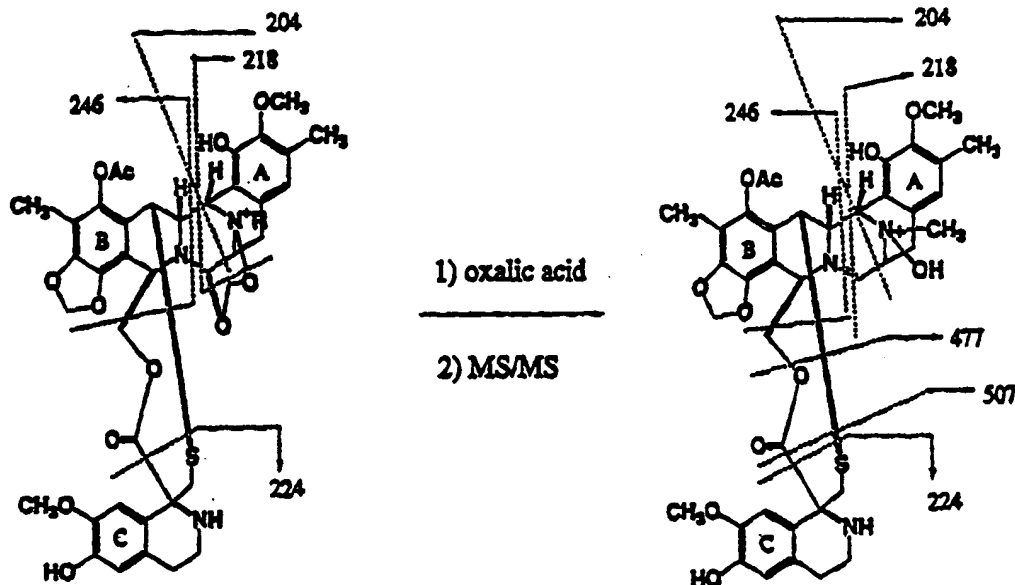




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(21) International Application Number: PCT/US98/07340 (22) International Filing Date: 14 April 1998 (14.04.98) (30) Priority Data: 60/043,596 15 April 1997 (15.04.97) US (71) Applicant: THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS [US/US]; 349 Administration Building, University of Illinois, 508 South Wright Street, Urbana, IL 61801 (US). (72) Inventors: RINEHART, Kenneth, L.; 454 Roger Adams Lab, 600 South Matthew Avenue, Urbana, IL 61801-3792 (US). ZHOU, Tong; 349 Administration Building, University of Illinois, 508 South Wright Street, Urbana, IL 61801 (US). (74) Agents: LINEK, Ernest, V. et al.; Dike, Bronstein, Roberts & Cushman, LLP, 130 Water Street, Boston, MA 02109-4280 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>

(54) Title: NUCLEOPHILE SUBSTITUTED ECTEINASCIDINS AND N-OXIDE ECTEINASCIDINS



(57) Abstract

Five new nucleophile substituted ecteinascidin (Et) compounds have been isolated from extracts of *Ecteinascidia turbinata*. These compounds have been purified by chromatographic techniques and their structures and bioactivities have been determined. The five nucleophile substituted Et compounds have been designated herein as Et 802 (1), Et 788 (2), Et 760 (3), Et 858 (4) and Et (815) (5). Also obtained were three new N-oxide ecteinascidin compounds, which have been designated herein as Et 717 (6), Et 775 (7) and Et 789 (8). Some of these newly discovered Et compounds show exceedingly potent cytotoxicity against L1210.

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NUCLEOPHILE SUBSTITUTED ECTEINASCIDINS
AND N-OXIDE ECTEINASCIDINS

BACKGROUND OF THE INVENTION

15 Ecteinasidins (Ets), exceedingly potent antitumor agents, first isolated
from the marine tunicate *Ecteinascidia turbinata*, especially Et 743, Et 729, Et
746 and Et 722 show significant efficacy *in vivo* against tumor cell lines
including P388 murine leukemia, B16 melanoma, Lewis lung carcinoma, and
human tumor xenograft models in mice.

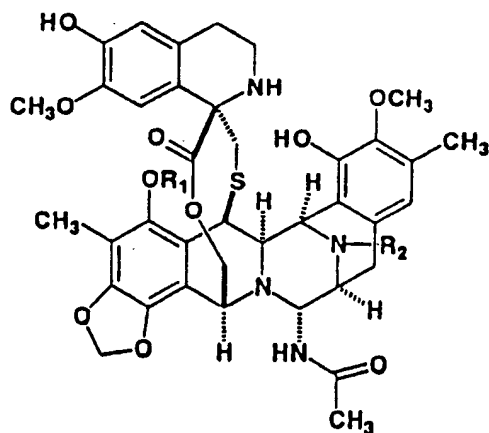
20 Continuing studies by Rinehart et al. are directed variously toward
providing adequate quantities of these compounds for clinical trials, study of
their antitumor mechanism of action, and determination of structure-activity
relationships. In addition, the discovery of additional Et compounds, whether
minor natural components or precursor compounds, will not only provide
25 evidence for their biosynthetic pathway, but should also be useful for with
respect to determining structure-activity relationships.

SUMMARY OF THE INVENTION

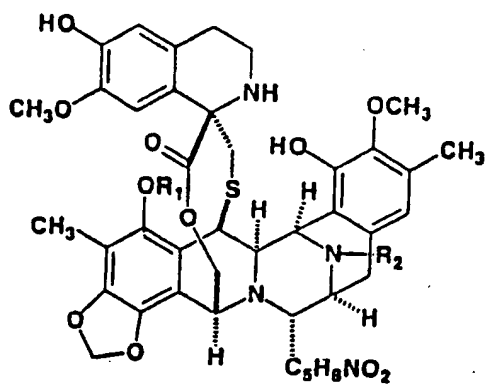
30 The present invention is directed to several newly discovered
ecteinascidin (Et) compounds, all isolated from extracts of *Ecteinascidia*
turbinata. For a detailed discussion of previously discovered ecteinascidin
compounds, as well as the methods used for their isolation and purification, see

Sakai et al., *J. Amer. Chem. Soc.*, **1996**, *118*, 9017, the disclosure of which is hereby incorporated herein by reference.

The structures of the new ecteinascidin compounds reported herein are
5 as follows:

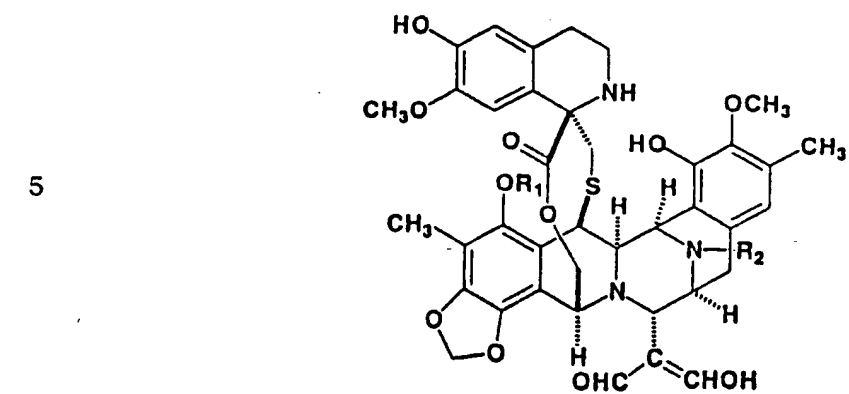


- 1: ET802, R1=Ac, R2=Me
2: ET760, R1=H, R2=Me
3: ET788, R1=Ac, R2=H

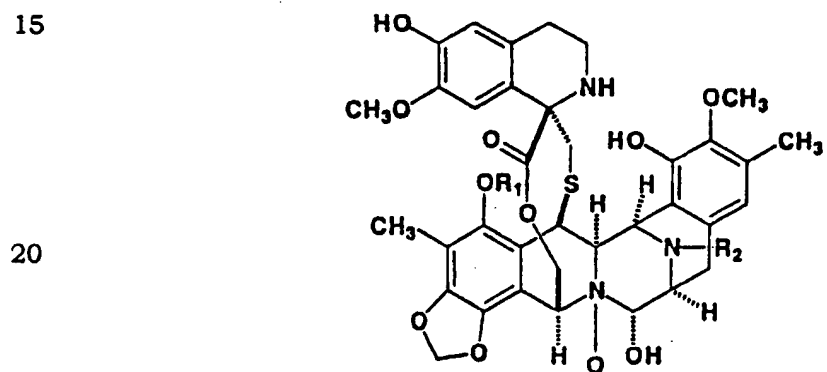


- 4: ET858 , R1=Ac, R2=Me**

- 3 -



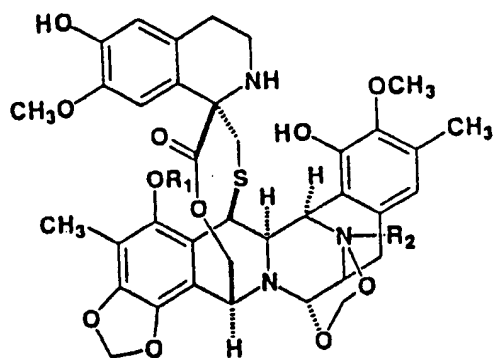
5: ET815, R1=Ac, R2=Me



6: ET717, R1=H, R2=Me

- 4 -

5

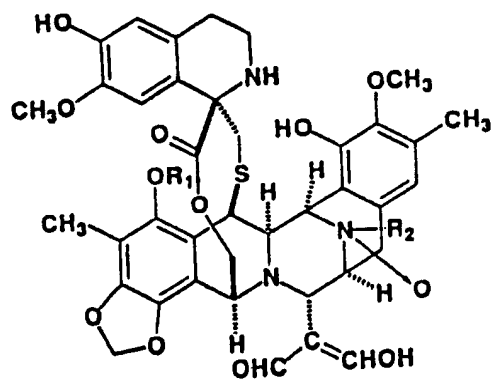


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7: ET776, R₁=Ac, R₂=H
8: ET789, R₁=Ac, R₂=Me
(fragment ET757)

15

20



25

9: ET832, R₁=Ac, R₂=Me
(fragment ET 813)

30

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates schematically the chromatographic processes used to isolate Et 717, Et 815, Et 813, Et 729 and Et 731 from extracts of *Ecteinascidia*
5 *turbinata*.

Figure 2 illustrates schematically the chromatographic processes used to isolate Et 729, Et 743, Et 788, Et 757, Et 789, Et 775, Et 745, Et 760, Et 802, Et 858 and Et 745 from extracts of *Ecteinascidia turbinata*.
10

Figure 3 illustrates schematically the chromatographic processes used to isolate Et 771, Et 759A, Et 743 and Et 729 from extracts of *Ecteinascidia turbinata*.

15 Figure 4 illustrates the MS/MS fragmentation of Et 802.

Figure 5 illustrates the MS/MS fragmentation of Et 760.

20 Figure 6 illustrates the MS/MS fragmentation of Et 788.

Figure 7A illustrates the MS/MS fragmentation of Et 858 and Figure 7B illustrates the MS/MS fragmentation of the fragment ion (m/z 800) thereof.

25 Figure 8 illustrates the MS/MS fragmentation of Et 717.

Figure 9A illustrates the MS/MS fragmentation of Et 789 (8, R = CH₃) and Et 775 (7, R = H) and Figure 9B illustrates the MS/MS fragmentation of the reaction product of Et 789 treated with oxalic acid.
30

DETAILED DESCRIPTION OF THE INVENTION

The five new nucleophile substituted ecteinascidin compounds, designated herein as Et 802 (1), Et 788 (2), Et 760 (3), Et 858 (4), Et 815 (5) and three new N-oxide ecteinascidins, designated herein as Et 717 (6), Et 775 (7) and Et 789 (8) were isolated and purified from extracts of *Ecteinascidia turbinata* by CCC, NP and RP column chromatography and RP-C18 HPLC as described in Figures 1-3.

The structures of the new Et compounds were assigned based on mass spectral data (HRFABMS, MS/MS fragmentation) and detailed analysis of 1D and 2D-NMR spectral data. Figures 4-9 illustrate MS/MS fragmentation for Et 802, Et 760, Et 788, Et 858, Et 717 and Et 789, respectively.

Spectral data for some of the new ecteinascidin compounds include the following:

Et 802 (1): HRFABMS: m/z 803.2962, M+H ion, $C_{41}H_{47}N_4O_{11}S$, $\Delta = 3.1$ mDa; 1H NMR, δ 4.15 (d, 1, H-1), 3.45 (br.d, H-3), 4.50 (br, H-4), 4.19 (dd, 1,2, H11), 3.09 (d, 12, H13), 2.98 (d, 15, H14a), 2.81 (dd, 12, 15, H14b), 6.46 (s, H15), 5.08 (dd, 2, 8, H21), 5.24 (d, 11, H22a), 4.01 (dd, 1, 11, H22b), 3.18 (ddd, H3'a), 2.78 (ddd, H3'b), 2.58 (ddd, H4'a), 2.30 (ddd, H4'b), 6.46 (s, H5'), 6.36 (s, H8'), 2.24 (d, 12, H12'a), 1.93 (d, 12, H12'b), 6.09 (s, -OCH₂O-), 6.03 (s, -OCH₂O-), 3.52 (s, 7'OMe), 3.66 (s, 17OMe), 2.25 (s, AcMe), 2.07 (s, NMe), 2.24 (s, 16Me), 1.96 (s, 6Me), 2.03 (s, NHCOMe).

Et 788 (2): HRFABMS: m/z 789.2806, M+H ion, $C_{40}H_{45}N_4O_{11}S$, $\Delta = 1.0$ mDa; 1H NMR, δ 4.21 (d, 1, H-1), 3.45 (br.d, H-3), 4.50 (br, H-4), 4.24 (dd, 1,2, H11), 3.09 (d, 12, H13), 6.48 (s, H15), 5.11 (dd, 2, 8, H21), 5.30 (d, 11, H22a), 4.01 (dd, 1, 11, H22b), 6.48 (s, H5'), 6.39 (s, H8'), 6.13 (s, -OCH₂O-), 6.07 (s, -

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OCH₂O-), 3.56 (s, 7'OMe), 3.67 (s, 17OMe), 2.25 (s, AcMe), 2.24 (s, 16Me), 1.96 (s, 6Me), 2.03 (s, NHCOMe).

Et 760 (3): HRFABMS: m/z 761.2856, M+H ion, C₃₉H₄₅N₄O₁₀S, Δ = 0.2
5 mDa; ¹H NMR, δ 4.15 (d, 1, H-1), 3.56 (br.d, H-3), 4.50 (br, H-4), 4.32 (dd, 1,2, H11), 3.09 (d, 12, H13), 3.00 (d, 15, H14a), 2.86 (dd, 12, 15, H14b), 6.52 (s, H15), 5.11 (dd, 2, 8, H21), 5.20 (d, 11, H22a), 4.01 (dd, 1, 11, H22b), 3.18 (ddd, H3'a), 2.78 (ddd, H3'b), 2.58 (ddd, H4'a), 2.30 (ddd, H4'b), 6.38 (s, H5'), 6.34 (s, H8'), 2.24 (d, 12, H12'a), 2.03 (d, 12, H12'b), 5.98 (s, -OCH₂O-), 5.85 (s, -
10 OCH₂O-), 3.54 (s, 7'OMe), 3.74 (s, 17OMe), 2.13 (s, NMe), 2.29 (s, 16Me), 2.06 (s, 6Me), 2.12 (s, NHCOMe).

Et 858 (4): HRFABMS: m/z 859.3192, M+H ion, C₄₄H₅₁N₄O₁₂S, Δ = 3.2
mDa; fragment ion m/z 800: m/z 800.2825, M+H ion, C₄₂H₄₆N₃O₁₁S, Δ = 2.8
15 mDa; Et 858, ¹H NMR, δ 4.13 (br.s, H-1), 3.41 (br.d, H-3), 4.50 (br, H-4), 4.36 (d, 3, H11), 2.79 (d, 13, H13), 3.01 (d, 12, H14a), 2.88 (dd, 12, 13, H14b), 6.50 (s, H15), 5.10 (d, 2, H21), 5.28 (d, 11, H22a), 4.09 (dd, 1.5, 11, H22b), 3.18 (ddd, H3'a), 2.62 (ddd, H3'b), 2.53 (ddd, H4'a), 2.45 (ddd, H4'b), 6.43 (s, H5'), 6.38 (s, H8'), 2.25 (d, 12, H12'a), 2.14 (d, 12, H12'b), 6.08 (s, -OCH₂O-), 5.98 (s, -
20 -OCH₂O-), 3.57 (s, 7'OMe), 3.73 (s, 17OMe), 2.28 (s, AcMe), 2.27 (s, 16Me), 2.01 (s, 6Me), 2.15 (s, NHCOMe), 2.09 (s, NHCOMe), 3.25 (NHCOMe), 2.64 (m, NHCOMe).

Et 717 (6): HRFABMS: m/z 718.2435, M+H ion, C₃₇H₄₀N₃O₁₀S, Δ = -0.1
25 mDa; ¹H NMR, δ 6.55 (H15), 6.44 (H8'), 6.38 (H5'), 6.07, 5.92 (-OCH₂O-), 5.78, 4.09 (H22a,b), 5.30 (H1), 5.19 (H21), 4.92 (H4), 4.57 (H11), 4.41 (H3), 3.64 (H13), 3.22, 2.91 (H14a,b), 3.00, 2.85 (H3'a,b), 2.61, 2.38 (H4'a,b), 3.74 (17-OCH₃), 3.54 (7'-OCH₃), 2.35 (6-CH₃), 2.27 (16-CH₃), 2.16 (N-CH₃).

30 Et 775 (7): HRFABMS: m/z 776, C₃₉H₄₂N₃O₁₂S, Δ = -0.0 mDa.

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Et 789 (8): HRFABMS: m/z 790, $C_{40}H_{44}N_3O_{12}S$, $\Delta = -0.2$ mDa; 12N-CH₃, δ 2.65 (singlet) observed in ¹H NMR.

Several of these new ecteinascidin compounds show exceedingly potent
5 cytotoxicity against L1210 (see Table 1).

TABLE 1

	Et Compound	IC ₅₀ ng/ml against L1210
10	Et 802 (1)	7
	Et 788 (2)	0.5
	Et 760 (3)	32
	Et 858 (4)	0.4
15	Et 815 (5)	0.4

As shown above, the present invention is directed to bioactive
compounds. These compounds have been prepared in substantially pure form,
20 i.e., at a purity level sufficient to allow physical and biological characterization
thereof. As described above, these compounds have been found to possess
specific antitumor activities and as such they will be useful as medicinal agents
in mammals, particularly in humans. Thus, another aspect of the present
invention concerns pharmaceutical compositions containing the active
25 compounds identified herein and methods of treatment employing such
pharmaceutical compositions.

The active compounds of the present invention exhibit antitumor activity.
Thus, the present invention also provides a method of treating any mammal
30 affected by a malignant tumor sensitive to these compounds, which comprises
administering to the affected individual a therapeutically effective amount of an

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active compound or mixture of compounds, or pharmaceutical compositions thereof. The present invention also relates to pharmaceutical preparations, which contain as active ingredient one or more of the compounds of this invention, as well as the processes for its preparation.

5

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules, etc.) or liquid (solutions, suspensions or emulsions) with suitable composition or oral, topical or parenteral administration, and they may contain the pure compound or in combination with any carrier or other pharmacologically active compounds. These compositions may need to be sterile when administered parenterally.

10

The correct dosage of a pharmaceutical composition comprising the compounds of this invention will vary according to the particular formulation, the mode of application, and the particular *situs*, host and bacteria or tumor being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

15

20

Several known ecteinascidin compounds, including Et 743 and Et 729 were also isolated, as shown below in Table 2.

25

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- 10 -

TABLE 2
Quantities of Et Compounds Isolated

	<u>Fraction A (550 mg)</u>	<u>Fraction B (261 mg)</u>	<u>Fraction C (40 mg)</u>
5	Et 729 39.4 mg	Et 729 31.6 mg	Et 743 10.2 mg
	Et 731 11.1 mg	Et 743 0.9 mg	Et 771 5.8 mg
	Et 745 45.4 mg	Et 745 6.0 mg	Et 759A 3.5 mg
	Et 759B 46.4 mg	Et 802 (1) 1.4 mg*	
	Et 597 3.4 mg	Et 788 (2) 0.2 mg*	
10	Et 717 (6) 2.6 mg*	Et 760 (3) 1.0 mg*	
	Et 815 (5) 5.1 mg*	Et 858 (4) 0.5 mg*	
	Et 814 (9) 5.9 mg*	Et 789 (8) 1.5 mg*	
		Et 775 (7) 0.5 mg*	

15 * - New Ecteinascidin Compounds

20 The present invention has been described in detail, including the preferred embodiments thereof. However, it will be appreciated that those skilled in the art, upon consideration of the present disclosure, may make modifications and/or improvements on this invention and still be within the scope and spirit of this invention as set forth in the following claims.

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CLAIMS:

1. Substantially pure Ecteinasidin 717, free of the cellular debris of *Ecteinasidia turbinata*.
5
2. Substantially pure Ecteinasidin 815, free of the cellular debris of *Ecteinasidia turbinata*.
3. Substantially pure Ecteinasidin 814, free of the cellular debris of *Ecteinasidia turbinata*.
10
4. Substantially pure Ecteinasidin 802, free of the cellular debris of *Ecteinasidia turbinata*.
5. Substantially pure Ecteinasidin 788, free of the cellular debris of *Ecteinasidia turbinata*.
15
6. Substantially pure Ecteinasidin 760, free of the cellular debris of *Ecteinasidia turbinata*.
20
7. Substantially pure Ecteinasidin 858, free of the cellular debris of *Ecteinasidia turbinata*.
8. Substantially pure Ecteinasidin 789, free of the cellular debris of *Ecteinasidia turbinata*.
25
9. Substantially pure Ecteinasidin 775, free of the cellular debris of *Ecteinasidia turbinata*.
10. A pharmaceutical or veterinary composition comprising an effective antitumor amount of the substantially pure compound designated
30

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herein as Et 717 and a pharmaceutically acceptable carrier, diluent or excipient.

11. A pharmaceutical or veterinary composition comprising an
5 effective antitumor amount of the substantially pure compound designated herein as Et 815 and a pharmaceutically acceptable carrier, diluent or excipient.

12. A pharmaceutical or veterinary composition comprising an
10 effective antitumor amount of the substantially pure compound designated herein as Et 814 and a pharmaceutically acceptable carrier, diluent or excipient.

13. A pharmaceutical or veterinary composition comprising an
15 effective antitumor amount of the substantially pure compound designated herein as Et 802 and a pharmaceutically acceptable carrier, diluent or excipient.

14. A pharmaceutical or veterinary composition comprising an
20 effective antitumor amount of the substantially pure compound designated herein as Et 788 and a pharmaceutically acceptable carrier, diluent or excipient.

15. A pharmaceutical or veterinary composition comprising an
25 effective antitumor amount of the substantially pure compound designated herein as Et 760 and a pharmaceutically acceptable carrier, diluent or excipient.

16. A pharmaceutical or veterinary composition comprising an
30 effective antitumor amount of the substantially pure compound designated

- 13 -

herein as Et 858 and a pharmaceutically acceptable carrier, diluent or excipient.

5 17. A pharmaceutical or veterinary composition comprising an effective antitumor amount of the substantially pure compound designated herein as Et 789 and a pharmaceutically acceptable carrier, diluent or excipient.

10 18. A pharmaceutical or veterinary composition comprising an effective antitumor amount of the substantially pure compound designated herein as Et 775 and a pharmaceutically acceptable carrier, diluent or excipient.

15 19. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated herein as Et 717 and a pharmaceutically acceptable carrier, diluent or excipient.

20 20. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated herein as Et 815 and a pharmaceutically acceptable carrier, diluent or excipient.

25 21. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated herein as Et 814 and a pharmaceutically acceptable carrier, diluent or
30 excipient.

- 14 -

22. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated herein as Et 802 and a pharmaceutically acceptable carrier, diluent or
5 excipient.

23. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated
10 herein as Et 788 and a pharmaceutically acceptable carrier, diluent or excipient.

24. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated
15 herein as Et 760 and a pharmaceutically acceptable carrier, diluent or excipient.

25. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated
20 herein as Et 858 and a pharmaceutically acceptable carrier, diluent or excipient.

25 26. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated herein as Et 789 and a pharmaceutically acceptable carrier, diluent or
30 excipient.

- 15 -

27. The use for the manufacture of a medicament for the therapeutic or prophylactic treatment of a patient suffering from a mammalian tumor, of an effective antitumor amount of the substantially pure compound designated herein as Et 775 and a pharmaceutically acceptable carrier, diluent or
5 excipient.

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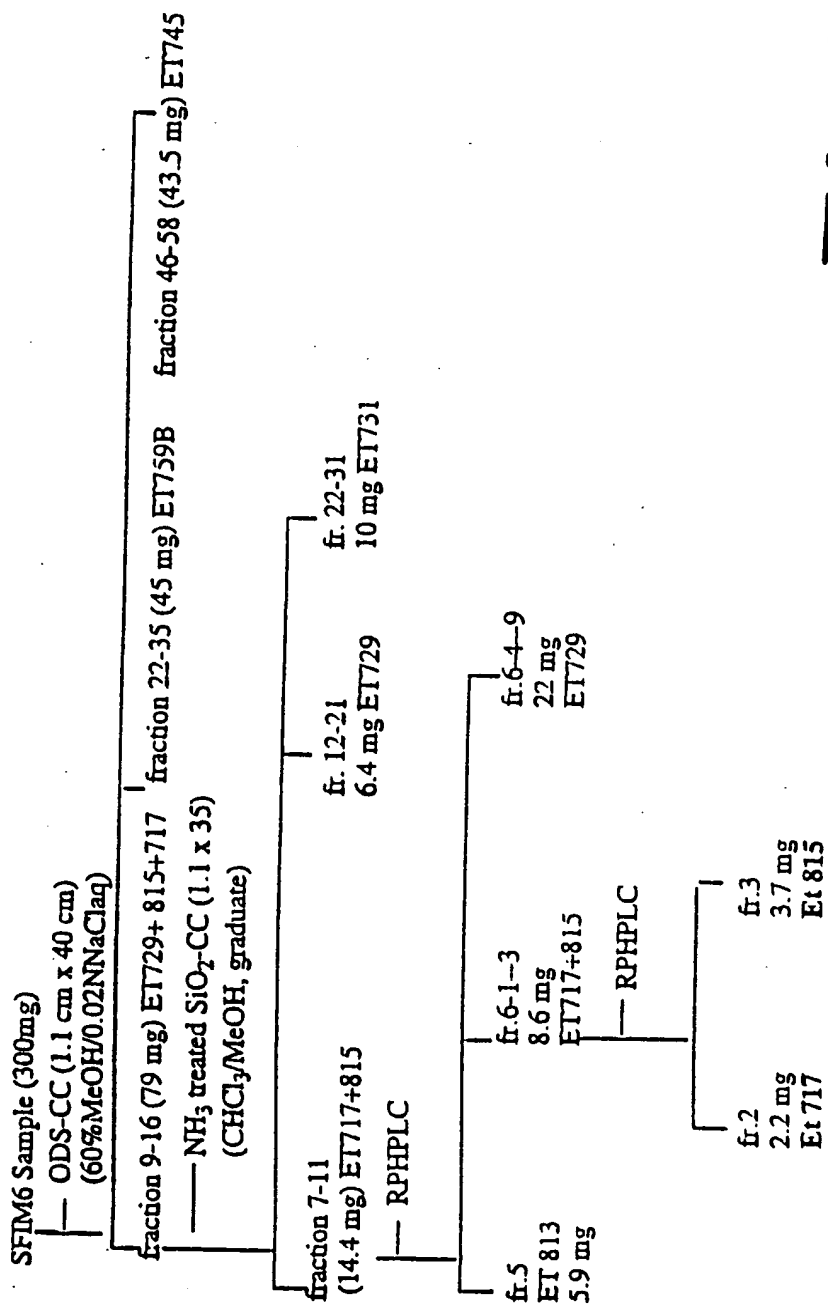


Fig. 1.

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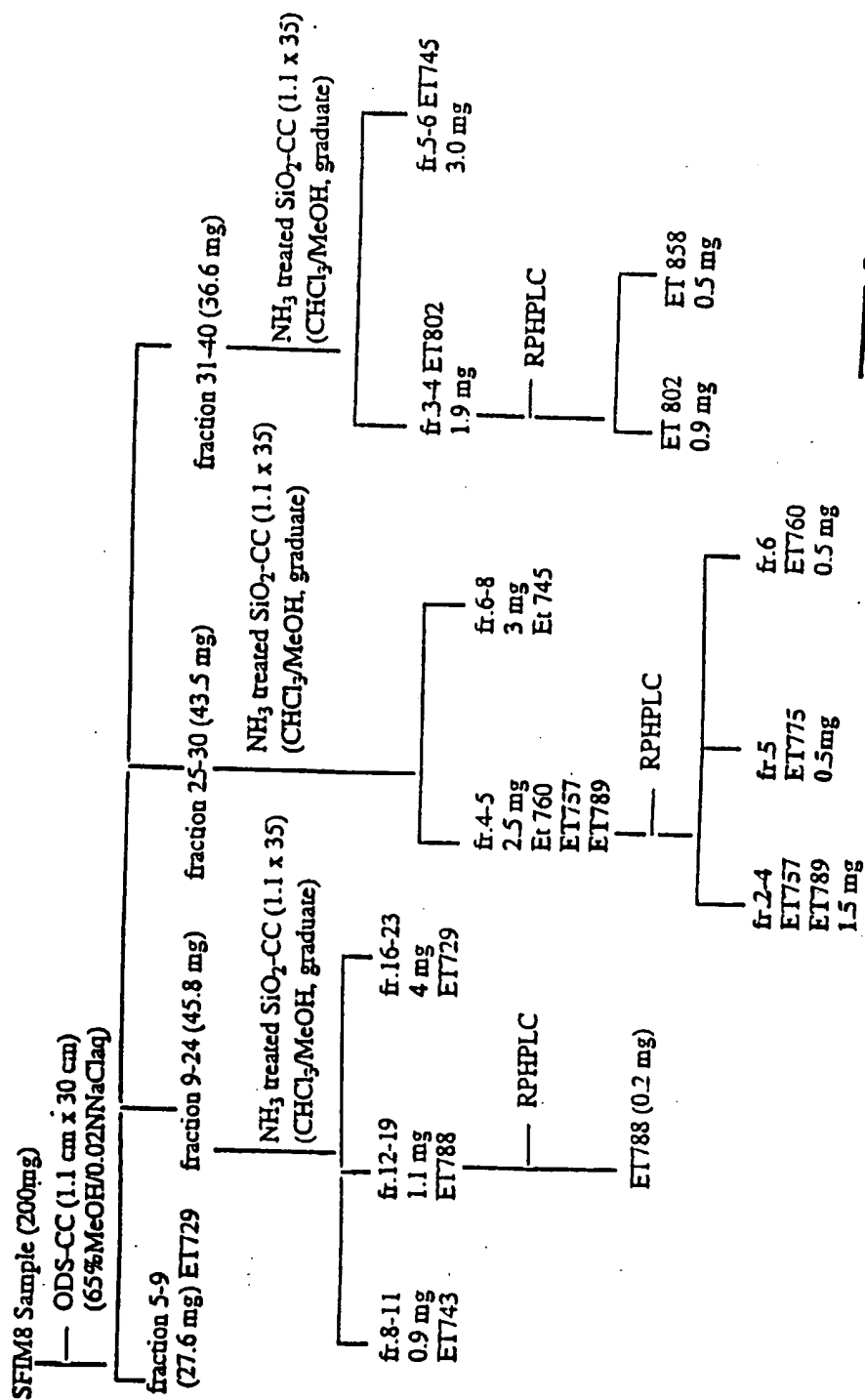


Fig. 2.

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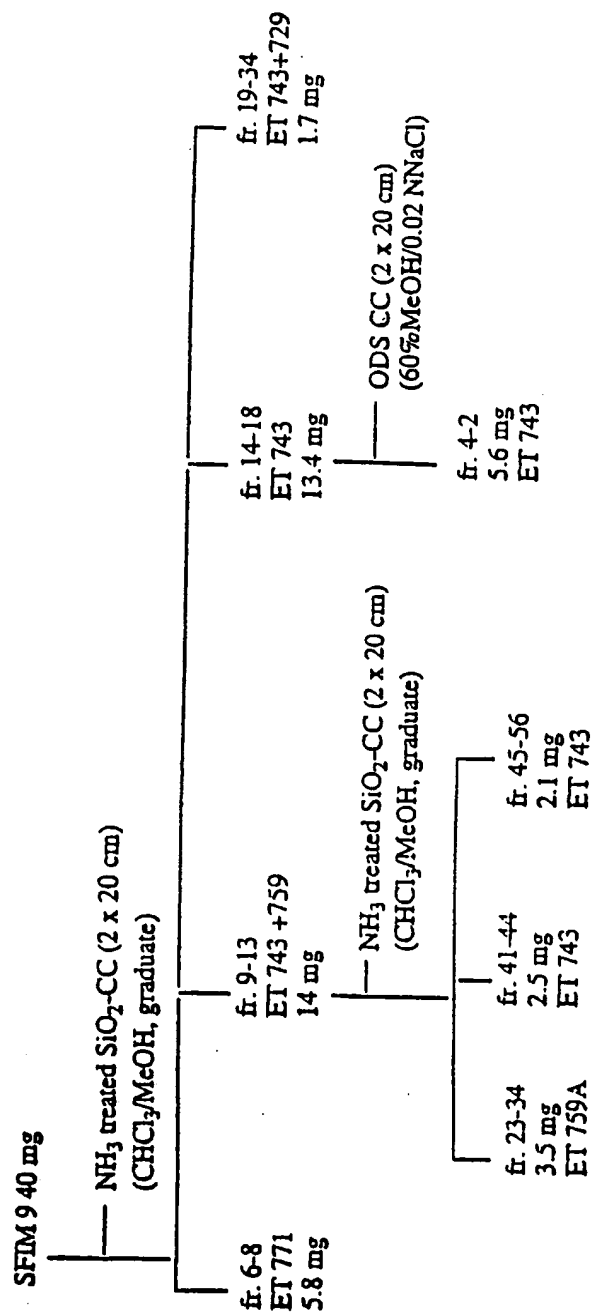


Fig. 3.

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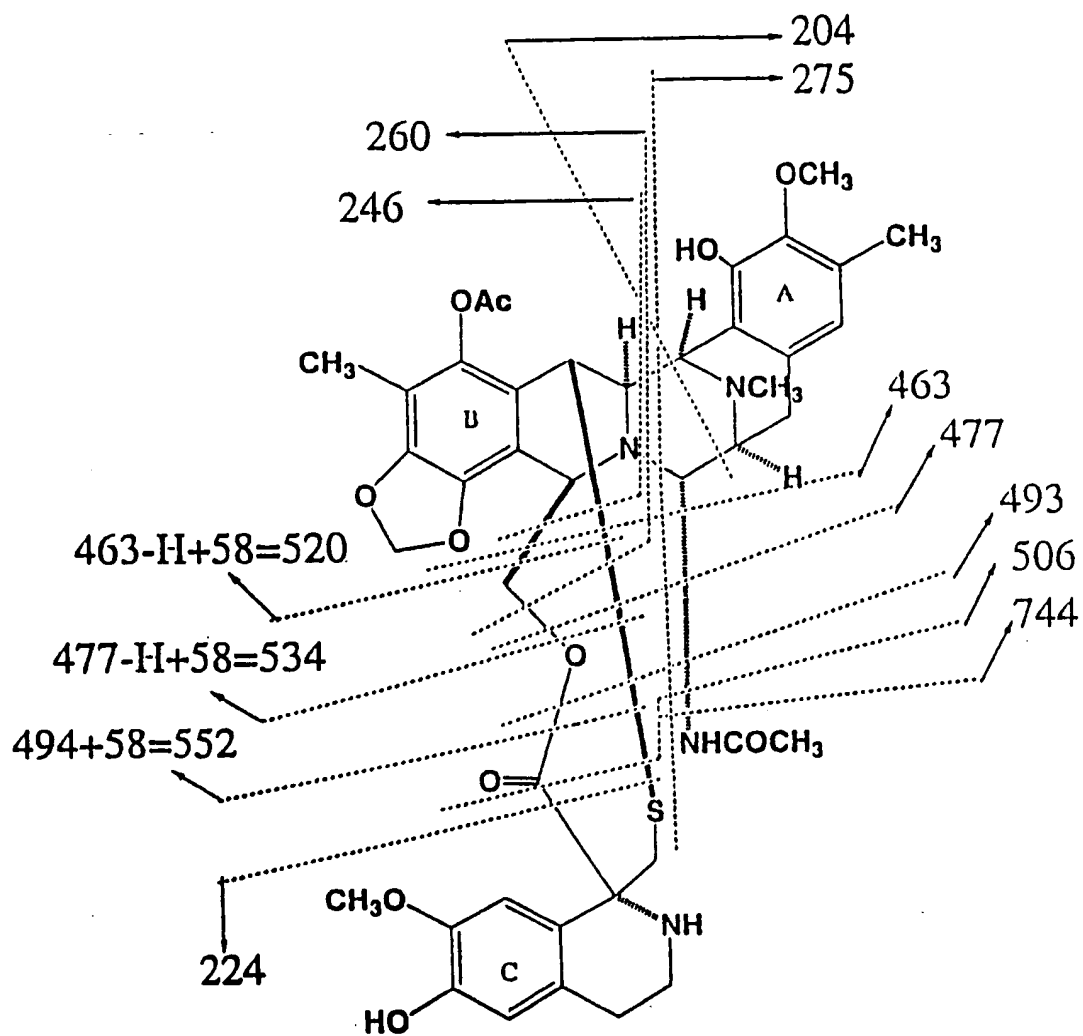


Fig. 4.

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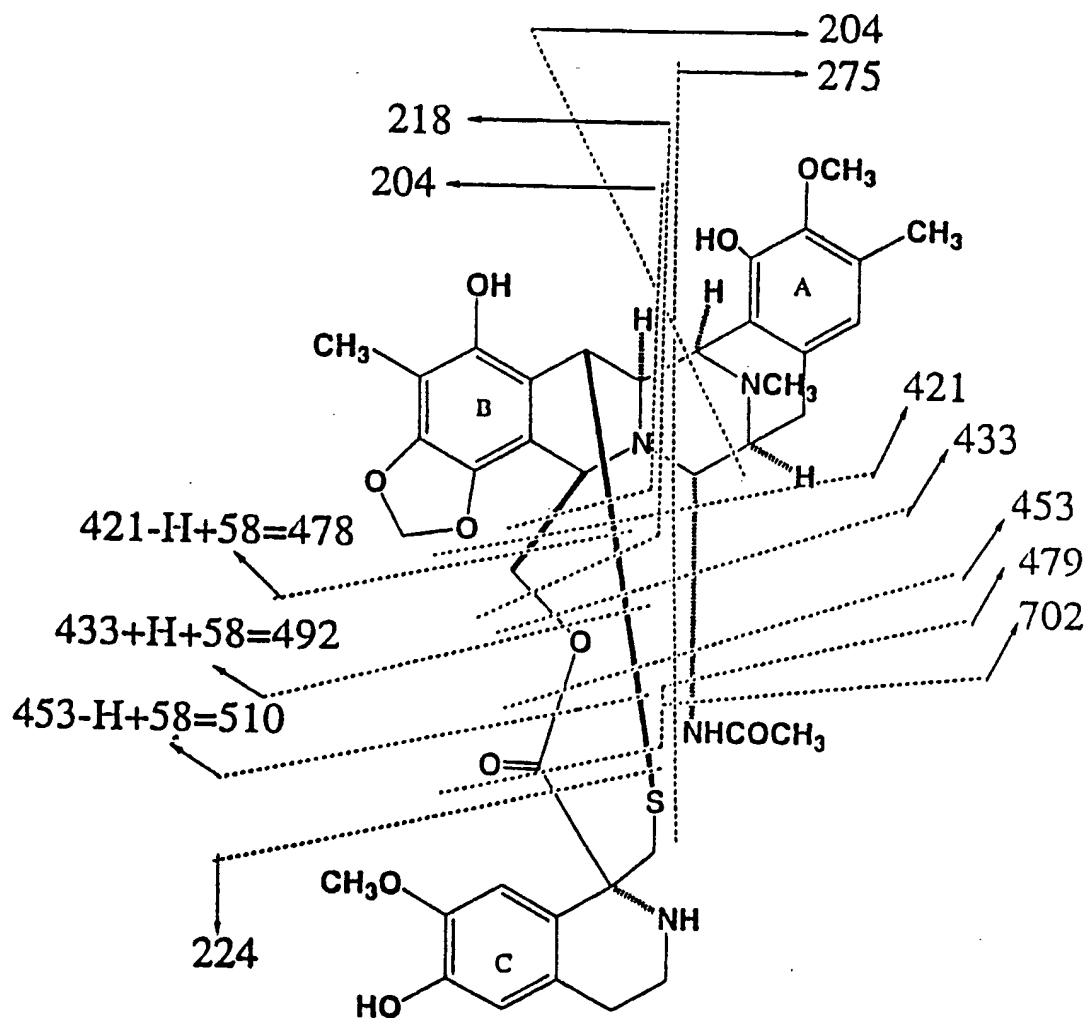


Fig. 5.

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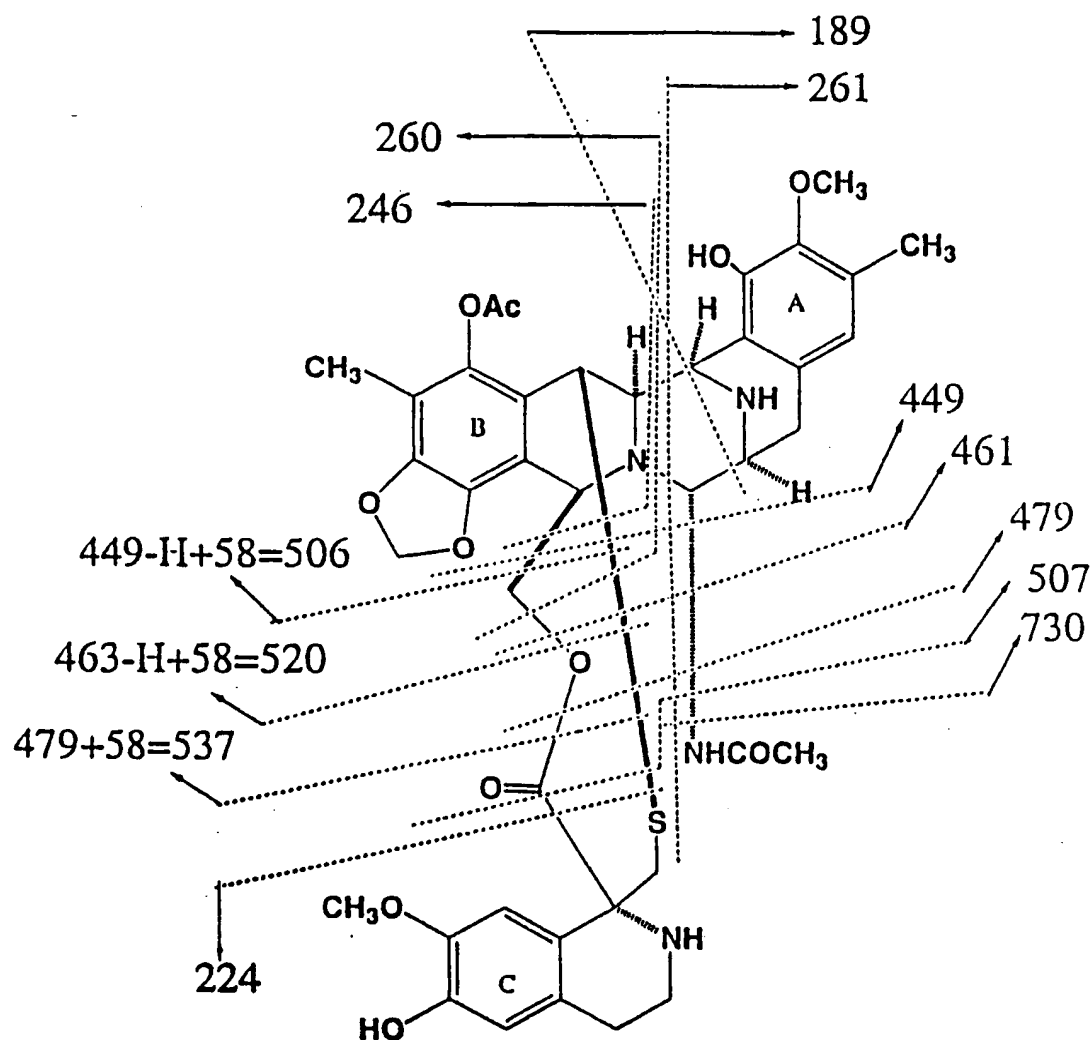


Fig. 6.

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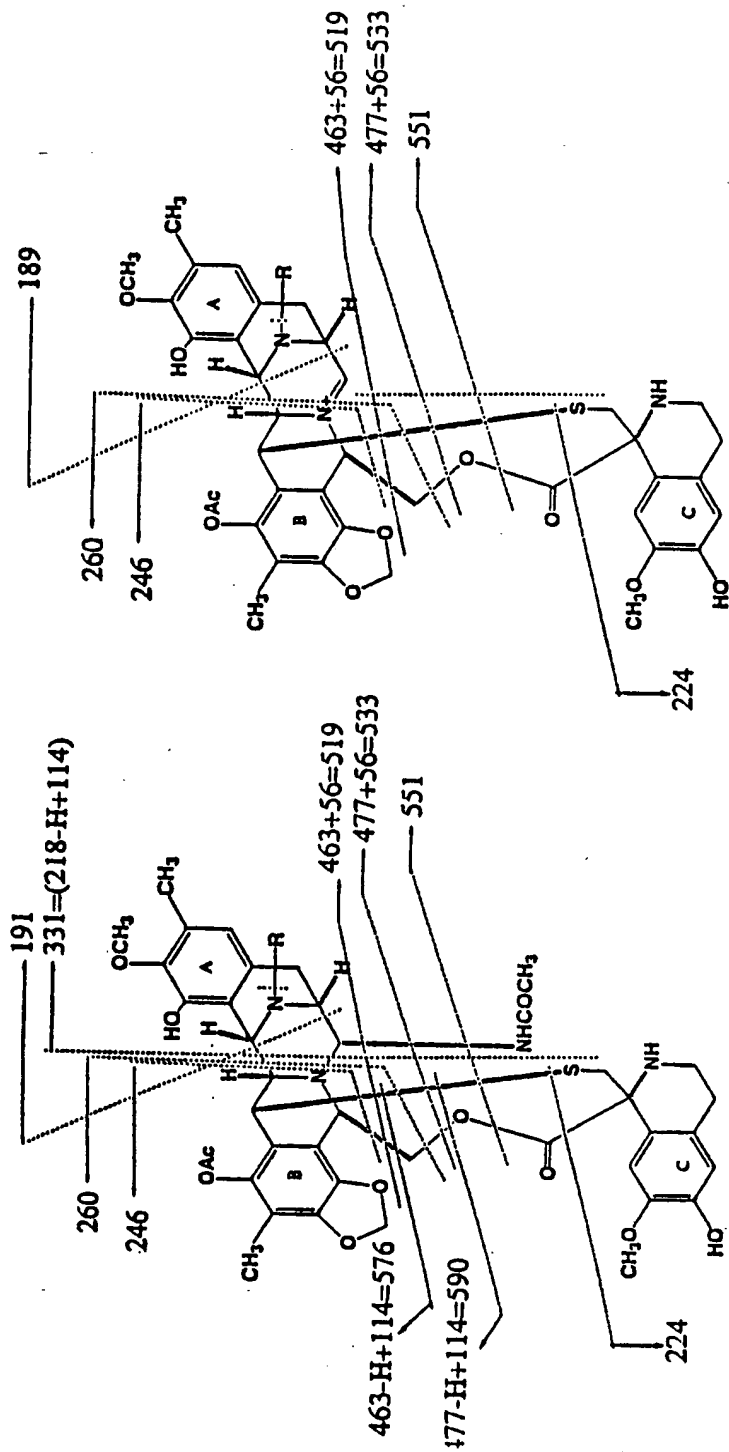


Fig. 7B.

Fig. 7A.

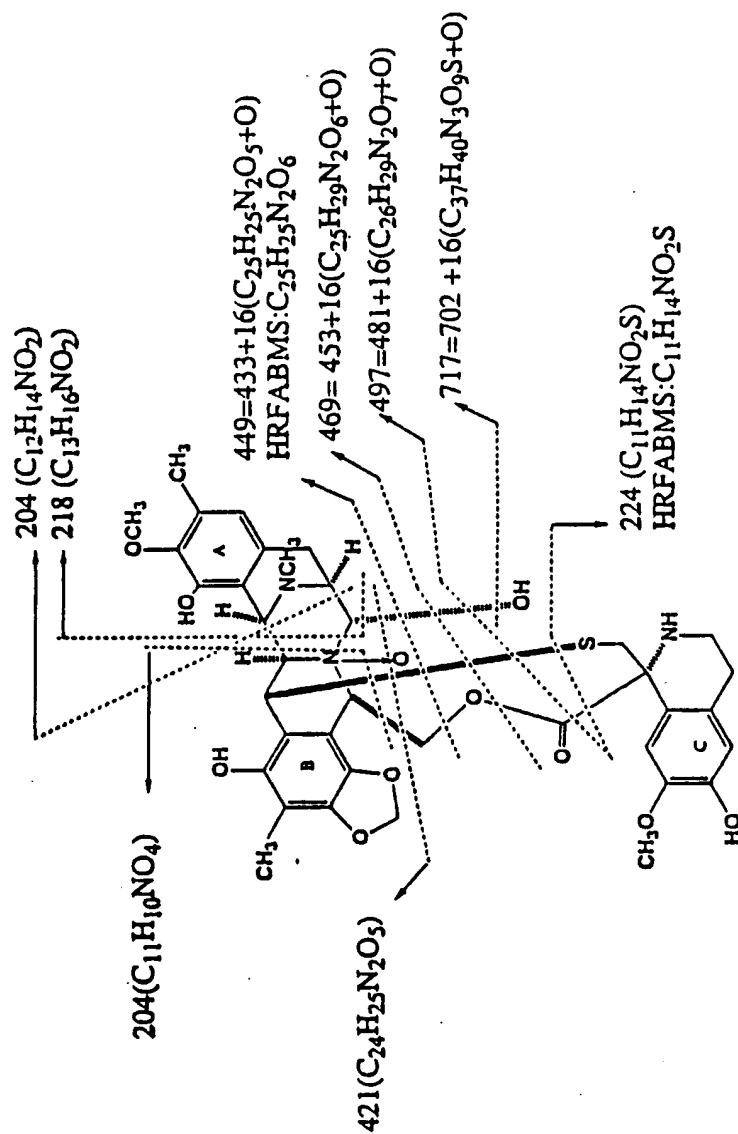


Fig. 8.

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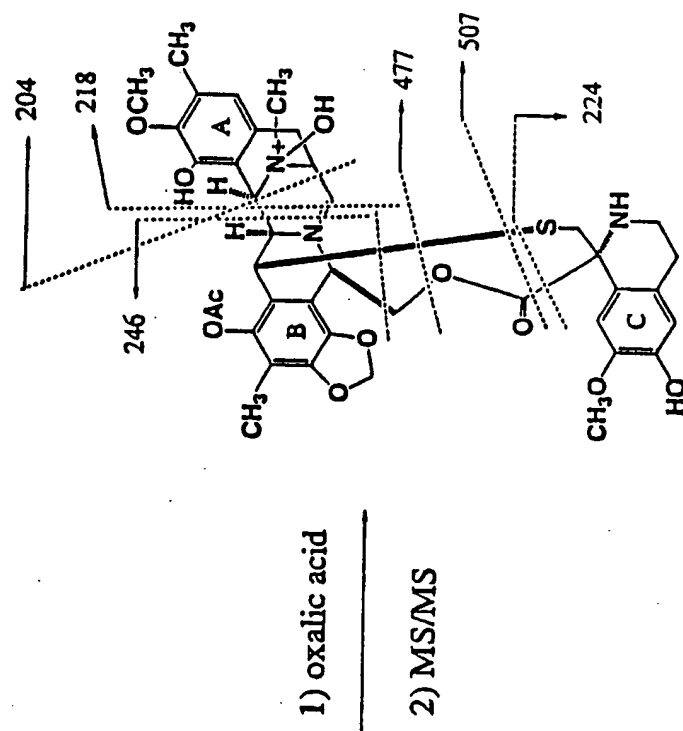


Fig. 9B.

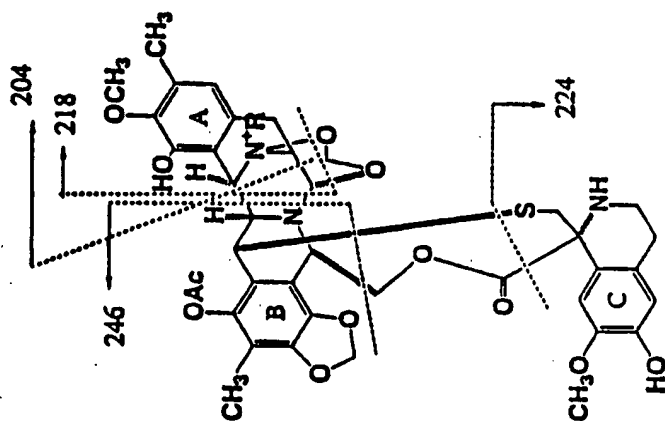


Fig. 9A.

INTERNATIONAL SEARCH REPORT

 International application No.
 PCT/US98/07340

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A01N 43/58; C07D 237/26, 241/36

US CL : 514/250; 544/233, 340

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/250; 544/233, 340

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,484,717 A (ZACCARDI) 16 January, 1996, col. 1 and 2.	1-27
A	US 5,459,141 A (VERTESY et al) 17 October 1995, abstract and col. 1.	1-27
A	US 4,273,773 A (DEMERSON et al) 16 June 1981, col. 1 and 2.	1-27

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

22 MAY 1998

Date of mailing of the international search report

21 JUL 1998

 Name and mailing address of the ISA/US
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